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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/487,558	01/19/2000	Robert Busby	109272.130	3300

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EXAMINER
LAMBERTSON, DAVID A

ART UNIT	PAPER NUMBER
1636	34

DATE MAILED: 07/15/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/487,558	BUSBY ET AL.	
	Examiner	Art Unit	
	David A. Lambertson	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *30 April 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *104-108,113,119-125,131-137,144-148 and 225-236* is/are pending in the application.

4a) Of the above claim(s) *120-125 and 131-137* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *104-108,113,119,144-148 and 225-236* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *19 January 2000* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Receipt is acknowledged of a reply, filed April 30, 2003 as Paper No. 33, to the Written Restriction Requirement mailed March 26, 2003 as Paper No. 32. Amendments were made to the claims in Paper No. 33. Specifically, claims 1-103, 109-112, 114-118, 126-130, 138-143 and 149-224 were cancelled, and new claims 226-236 were added.

Claims 104-108, 113, 119-125, 131-137, 144-148 and 225-236 are pending in the instant application. Claims 120-125 and 131-137 are withdrawn as being drawn to a non-elected invention, with traverse. Claims 104-108, 113, 119, 144-148 and 225-236 are ready for examination in the instant application.

Election/Restrictions

Applicant's election with traverse of Group I (claims 104-108, 113, 119-125, 131-137, and 144-148) in Paper No. 33 is acknowledged. The traversal is on the ground(s) that: (A) conditionally expressing and overexpressing a gene both relate to the expression level of a gene, therefore the methods of conditionally expressing and overexpressing a gene are not unrelated and should be searched together; (B) it would be more efficient to examine methods of conditionally expressing and overexpressing a gene for the production of a polyketide together; (C) that cells overexpressing or conditionally expressing a gene (and methods of making these cells) are closely related to methods of producing a polyketide by conditionally expressing and overexpressing a gene, and should therefore be examined together with the methods. Upon further consideration and in view of applicant's arguments (specifically parts A and B listed above), the examiner agrees to the rejoinder of Groups I and II (new claims 225-236). However,

the traversal of the restriction of Groups VI and VII (part C listed above) is not found persuasive because of the following reasons:

The cells overexpressing or conditionally expressing a gene (and methods of making these cells) are patentably distinct from methods of producing a polyketide using these cells because art reading on the cells does not necessarily result in art reading on the methods for producing polyketides, thus the inventions have different scopes. For example, the cells overexpressing or conditionally expressing a gene could easily be used for the recombinant production of the gene, rather than the production of a polyketide. Thus the inventions are clearly distinguishable as product and process of using, whereby the product can be used for a patentably distinct process.

The requirement is still deemed proper and is therefore made FINAL.

Drawings

New corrected drawings are required in this application because of the reasons set forth in the Draftspersons review for PTO-948, attached to Paper 9. Applicant is advised to employ the services of a competent patent draftsperson outside the Office, as the U.S. Patent and Trademark Office no longer prepares new drawings. The corrected drawings are required in reply to the Office action to avoid abandonment of the application. The requirement for corrected drawings will not be held in abeyance (see 37 CFR 1.85(a)).

Because the Examiner recalls that there was some difficulty concerning the instant application during a change in power of attorney, the Examiner is including a photocopy of the previous PTO-948 with this Office Action.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 104-108, 113, 119, 144-148 and 225-236 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The test of enablement is whether one skilled in the art could make and use the claimed invention from the disclosures in the specification coupled with information known in the art without undue experimentation (*United States v. Telectronics.*, 8 USPQ2d 1217 (Fed. Cir. 1988)). Whether undue experimentation is needed is not based upon a single factor but rather is a conclusion reached by weighing many factors. These factors were outlined in *Ex parte Forman*, 230 USPQ 546 (Bd. Pat. App. & Inter. 1986) and again in *In re Wands*, 8 USPQ2d 1400 (Fed. Cir. 1988) the most relevant of which are discussed below:

Nature of the invention. The nature of the invention is a method of producing polyketides by overexpressing or conditionally expressing a *creA* gene in a filamentous fungi. The invention involves metabolic engineering of every pathway involved in the synthesis of all polyketides.

Scope of the invention. The scope of the invention is very broad, encompassing the production of a large number of polyketides, many of which are not produced by fungi because the specific

enzymes required for their production, polyketide synthases (a.k.a., PKS), are not present in the organism.

State of the art. The state of the art clearly indicates that the metabolic engineering of strains to produce polyketides is very demanding in that it requires the functional expression of a large number of enzymes for each type of polyketide, the presence of appropriate amounts of precursors for their production, as well as the ability of the host cells to produce large quantities of the desired polyketide without toxicity to the host cell (see for example Pfeifer *et al.*, Micro. Mol. Biol. Rev. 65: 106-118, March 2001; see entire reference, e.g. the paragraph bridging pages 106-107). For example, Figure 2 of Pfeifer *et al.* (see for example page 108) lists some common polyketides, and their natural production hosts; there is no expectation that compounds such as Actinorhodin or Erythromycin could be generated in fungi without the transfer of a complete set of the corresponding PKS genes into the host organism. Even then, the metabolic engineering of cells is unpredictable, as set forth in Parekh *et al.* (reference cited in the previous Office Actions, and applied as such in the instant action). To briefly reiterate, Parekh teaches that the overproduction of secondary metabolites requires precision in the manipulation of the host cell, taking into consideration the physiology of the host cell and the regulatory pathway (i.e., the PKS pathway) being manipulated, including any potential feedback mechanism endogenous to the host cells that are chosen. Parekh concludes that "...with only limited knowledge of the physiology and the genetics associated with the production of each molecule of interest, one is often led to an empirical approach to strain improvement" (see for example page 288, left column). In short, the prior art provides no direction as to the production of all polyketides in a fungal host cell simply by overexpressing or conditionally expressing a single gene, *creA*.

Rather, the prior art indicates that without specific instructions and examples, the skilled artisan would be reduced to practicing undue and unpredictable trial and error experimentation as it regards the production of any polyketide in any fungal cell. Therefore, the skilled artisan could not rely on the prior art for guidance as it regards the claimed invention.

Number of working examples and Guidance provided by applicant. The instant specification provides no guidance or working examples as it regards the use of *creA* overexpression or conditional expression in fungal cells for the production of any polyketide. The *creA* gene is simply provided in a laundry list of genes that can be allegedly overexpressed or conditionally expressed in a fungal cell, thereby resulting in the production of any polyketide. There is no indication in the specification as to how to overexpress or conditionally express the *creA* gene, what medium and/or culture conditions must be used to produce a polyketide, or what polyketides can be produced in response to this overexpression/conditional expression. The specification merely makes a prophetic claim, saying that the overexpression/conditional expression of any one of a number of genes can result in the production of any polyketide. As a result, the skilled artisan cannot consult the instant specification for guidance on how to practice the claimed invention.

In response to a previous Office Action, a declaration under 37 CFR 1.132 was provided and considered. The examiner would like to focus attention on Example 1 of the declaration as it relates specifically to the claimed invention. The example indicates that the fungus *A. terreus* was transformed with the plasmid MB1301, indicated to express *creA*, and grown under specific conditions, thereby resulting in an increased production of lovastatin relative to a strain transformed with the plasmid MB2143. This declaration fails to overcome the enablement

rejection because the details provided by the declaration do not have reasonable support in the specification. The specification does not describe either plasmid MB1301 or MB2143 in the specification so that the skilled artisan would be apprised to use these plasmids, or plasmids like them, in the claimed invention. In addition, the skilled artisan would not be able to determine if the *creA* gene was indeed the determining factor in the increased production of lovastatin because there is no indication of what if any other important elements are included on the recited plasmids, or whether or not these plasmids are comparable (in as much as one serves as an appropriate control for the experiments conducted). Furthermore, this single example is not indicative that overexpression of *creA* from any plasmid, or other source, is sufficient to produce lovastatin. In addition to not being apprised of the particular plasmids, the skilled artisan would also be unaware of the media conditions that are required for the production of lovastatin as indicated in the declaration, because these specific conditions are not disclosed in the instant specification. Thus, the declaration improperly tries to incorporate information that is necessary to practice the claimed invention, but that was not included in the instant specification. Therefore, the declaration cannot overcome the enablement rejection.

Level of skill in the art. The level of skill in the art is highly underdeveloped, which is clearly set forth in the Parekh and Pfeifer references cited above in the State of the Art section of the enablement rejection. The level of skill is deficient in terms of the pathways to be manipulated, the products to be produced, etc., as set forth above.

Unpredictability of the art and Amount of experimentation required. In order to practice the claimed invention, the skilled artisan would be armed with only the instant specification and the teachings of the prior art at the time of the invention. The prior art teaches that metabolic

engineering is unpredictable, and that the manipulation of a pathway for the production of a particular compound requires explicit instructions regarding the particular pathway and product to be made. Pfeifer further teaches that this is true for polyketides, specifically, and that knowledge of the particular PKS pathway enzymes and their manipulation is absolutely necessary for the engineered production of polyketides. Thus, the skilled artisan would be forced to rely on the instant specification for the particular teachings regarding the production of polyketides by overexpressing/conditional expression *creA* in a fungal cell. However, the specification provides no specific teachings regarding the overexpression or conditional expression of *creA* for the production of any polyketides in a fungal cell. Rather, the specification merely suggests the overexpression or conditional expression of a laundry list of genes, including *creA*, and that this overexpression/conditional expression will result in the production of any polyketide. The specification provides no scientific correlation between *creA* and any particular polyketide synthesis pathway, and provides no examples that the overexpression or conditional expression of *creA* results in an increased production of a polyketide. Finally, the conditions required for the production of lovastatin (e.g., media conditions) are absent from the specification. The skilled artisan, seeking to practice the claimed invention, would be reduced to randomly searching for overexpression/conditional expression conditions and media conditions for different polyketides with the hope that he would stumble onto the appropriate conditions for the production of a particular polyketide. Thus, the skilled artisan would be forced to practice undue and unpredictable trial and error experimentation when practicing the claimed invention.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 104-108, 113, 119, 144-148 and 225-236 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Specifically, the claims fail to recite a positive process step that refers back to the preamble of the claim. For instance, there is no method step wherein a polyketide is produced, therefore the claimed method has no terminal step and thus the metes and bounds of the claimed method are indefinite. Indicating a step in the claimed method such as "whereby a polyketide is produced" would be remedial.

Allowable Subject Matter

No claims are allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David A. Lambertson whose telephone number is (703) 308-8365. The examiner can normally be reached on 6:30am to 4pm, Mon.-Fri., first Friday off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel, Ph.D. can be reached on (703) 305-1998. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 305-3014 for regular communications and (703) 305-3014 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

David A. Lambertson
July 11, 2003

PATENT EXAMINER
A.U. 1636